the above-described amendments. Claims 28, 30-37, 61-69, and 75-88 are now pending. The rejections set forth in the Office Action have been overcome by amendment or traversed by argument below.

The specification was objected to for lacking a title for the description of the drawings, and it was suggest that tables 1 and 2 on page 12 of the specification be deleted and added as drawings. In this response, Applicants have amended the specification to add a title for the description of the drawings and to delete Tables 1 and 2. Applicants have amended the drawings to submit Tables 1 and 2 as Figures 17 and 18. Applicants therefore respectfully request that the objections to the specification be withdrawn.

Claims 47 and 59 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In this response, Applicants have cancelled claims 47 and 59. Thus, this ground of rejection has become moot, and Applicants respectfully request that it be withdrawn.

Claims 25-64, 66-78, and 80-86 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bolesak *et al.* (U.S. Patent No. 5,100,662) in view of Gao *et al.*, 1991. *Biochem. Biophys. Res. Comm.* 179:280-85. These claims also stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Popescu *et al.* (European Patent No. 0 356 339) in view of Epand *et al.* (U.S. Patent No 5,283,185). In addition, claims 65 and 79 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over either Bolesak *et al.* in view of Gao *et al.* or Popescu *et al.* in view of Epand *et al.*, further in view of del Prete *et al.*, 1994, *Trends Microbiol.* 2:4-6. The Examiner contends that it would have been *prima facie* obvious to one of skill in the art to substitute the liposome formulations taught by either Gao *et al.* or Epand *et al.* for the vaccine

compositions taught by either Bolesak *et al.* or Popescu *et al.* for increased stability and decreased toxicity. Applicants respectfully disagree.

The presumption that one would substitute the liposome formulations of Gao *et al.* or Epand *et al.* for those of Bolesak *et al.* or Popescu *et al.* is based on the unstated, but implied assumption Gao *et al.*'s and Epand *et al.*'s liposome formulations would be good adjuvants. (If they were not good adjuvants, *i.e.*, they were ineffective at increasing immunogenicity of the antigens, it would be immaterial that they had increased stability and decreased toxicity since they would not serve the intended purpose.) In fact, the Examiner's assumption is far broader implying that all liposomes can be utilized as adjuvants in vaccine formulations. This assumption, however, is false, finding no support in the cited art.

Despite a few demonstrations of particular liposome formulations as immunological adjuvants it is quite clear that all liposome formulations are not useful as adjuvants in vaccine formulations. Numerous factors, such as vesicle size, surface charge, lipid composition, phase transition temperature of the lipid comprising the liposome, lamellarity, antigen localization (whether or not there is encapsulation of the antigen or whether the antigen is present on the liposomal surface), modes of administration and fusogenicity have been identified as contributing qualitatively and quantitatively to differences in adjuvanticity of liposomal preparations (Kersten & Crommelin, Biochim. Biophys. Acta (1995) 1241:117-138). Significantly, however, the manner in which these factors contributes to adjuvanticity is unpredictable and no formula exists that would permit one of ordinary skill in the art to determine *a priori* whether a particular liposomal preparation (and, in particular, the claimed liposomal preparations) would be an adjuvant ("It is not a clear picture that emerges from the cited studies" Kersten p. 122). Furthermore, the Applicants are unaware of any teachings in the

prior art from which one of ordinary skill could have determined with a reasonable degree of assuredness that the claimed liposomal formulations would be good adjuvants. In particular, the vaccine compositions of the present invention employ a compound, dc-Chol, which is positively charged. The US Patent No. 4,053,585 col. 1 lines 42-47 teaches that: "Adjuvant preparations based on negatively charged liposomes elicit the formation of much higher concentrations of antibodies than are elicited by the use of free antigen. On the other hand, antigens entrapped in positively charged liposomes elicit less antibody than the same dose of free antigen." Therefore, US Patent No. 4,053,585 teaches that positively charged liposomes do not work as adjuvants. (*See also,* col. 2 lines 36-38). Further, in Tyrrell et al. (1976) Biochimica et Biophysica Acta 457: 257-302 the authors state: "In addition to liposomes containing more than 30% cholesterol, a number of other lipid compositions have shown to have little or no adjuvant effect on the antigen concerned. Allison & Gregoriadis conclude that positively charged liposomes (7:2:1 phosphatidyl choline: cholesterol: stearylamine) do not exert an adjuvant effect on the antigen diptheria toxoid..." (p.290). Even today the literature contains information that indicate that many liposomal formulations are ineffective as adjuvants. Haan et al. (2000) J. Liposomal Res. 10: 150-177 indicate that "negatively charged liposomes, **but not positively charged or zwitterionic liposomes**, coadministered i.n. with influenza subunit antigen, significantly stimulated system IgG level and local antibody responses in pulmonary secretions, relative to the responses upon i.n. administration of subunit antigen alone" p. 159. The liposomes of the present invention are cationic and thus, according to this recent publication, would be ineffective as an adjuvant. Therefore, one of ordinary skill in the art could not have had a reasonable expectation of successfully obtaining the presently claimed invention and, thus, the claims cannot be obvious.

CONCLUSIONS

Applicants believe that the rejection under 35 U.S.C. § 112, second paragraph, has been overcome by amendment. Applicants further contend that the rejections under 35 U.S.C. § 103(a) should be withdrawn because the prior art relied upon neither teaches nor suggests the presently claimed invention; furthermore, one of ordinary skill in the art could not have reasonably expected to successfully obtain the presently claimed invention. Allowance of the claims is therefore respectfully solicited.

Respectfully submitted,

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Redlined Version of Claim Amendments

28. (Twice Amended) The vaccine composition of claim [25] 30, wherein said antigen is influenza antigen.

30. (Twice Amended) [The] A vaccine composition [of claim 26] comprising at least one antigen and [wherein said amphipathic adjuvant compound is selected from the group consisting of: cholesteryl-3-E-carboxyamidoethylenetrimethylammonium iodide, cholesteryl-3-E-carboxyamidoethylenamine, cholesteryl-3-E-oxysuccinamidoethylene-trimethylammonium iodide,] 3-E-(N-(N-N'-dimethylaminoethane)carbamoyl) cholesterol [, and 3-E-(N-(N-N'-polyethylenlamine)carbamoyl) cholesterol].

33. (Twice Amended) The vaccine composition of claim [25] 30, further comprising a neutral lipid.

36. (Twice Amended) The vaccine composition of claim [25] 30, wherein said [amphipathic adjuvant compound] 3-E-(N-(N-N'-dimethylaminoethane)carbamoyl) cholesterol is dispersed in an aqueous environment in the form of liposomes.

37. (Twice Amended) The vaccine composition of claim [25] 30, wherein said 3-E-(N-(N-N'-dimethylaminoethane)carbamoyl) cholesterol [amphipathic adjuvant compound] takes the form of liposomes including at least one antigen.

62. (Twice Amended) A method of inducing an immune response in a mammal, comprising administering the vaccine composition of claim [25] 30, to a mammal.

75. (Twice Amended) A method of inducing an immune response in a mammal, comprising

(a) administering at least one antigen to a mammal; and

(b) further administering [at least one amphipathic adjuvant compound comprising a lipophilic group derived from a sterol linked to a polar group via a carbamoyl group] the vaccine composition of claim 30, to a mammal.